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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/194,053	11/23/1998	MOHAMED CHOKRI	USB96AKIDM	2743

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EXAMINER
EWOLDT, GERALD R

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1644	31

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/194,053	Applicant(s) Chokri et al.
	Examiner G.R. Ewoldt	Art Unit 1644

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Jan 29, 2003* .

2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *44, 46, 47, 49-51, 53-55, 60, 61, and 88* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *44, 46, 47, 49-51, 53-55, 60, 61, and 88* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☒ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 28
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. Applicant's amendment and remarks, filed 1/29/03 are acknowledged.

2. Claims 45 and 58 have been canceled.
Claim 88 has been added.
Claims 44, 46, 47, 49-51, 53-55, 60, 61 and 88 are pending and being acted upon.

3. In view of Applicant's Amendments and Remarks, filed 1/29/03, the previous rejections under the second paragraph of 35 U.S.C. 112, and the first paragraph of 35 U.S.C. 112 (for the introduction of new matter into the claims), have been withdrawn.

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 44, 46-47, 49-51, 53-55, and 60-61, and newly added Claim 88, stand/are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, for the reasons of record as set forth in Paper No. 26, mailed 7/29/02.

Applicant's arguments, filed 1/29/03, have been fully considered but they are not persuasive. Applicant argues that "Applicants respectfully submit that present specification discloses to one of ordinary skill in the art how to make the claimed MD-APCs and that the claimed MD-APCs exist as a single, specific, cell type. The claimed MD-APCs may be obtained according to the process of the present invention. The Examiner's attention is respectfully directed to page 5, lines 37 to page 8, line 9."

As set forth previously, it is the Examiner's position that it is unclear just what the product of the method of the specification consists of. Specifically, it is unclear whether the method results in a discrete cell type comprising both increased phagocytic capacity and antigen presentation ability or

a mixture of cells, some displaying phagocytic capacity and some displaying antigen presentation ability.

Applicant has submitted two references, Boyer et al. and Chaperot et al. which Applicant argues teach that the MD-APCs of the instant claims do indeed exist. Applicant continues by summarizing similarities in the methods and products of the references to the methods and products of the instant specification and claims.

It is noted, however, that the methods of producing the cells of the references are not the methods of the instant specification and claims, and the cells of the references display different cell surface markers than the cells of the instant claims. For example, neither of the references teach a method of producing MD-APCs comprising the use of histamine and cimetidine, i.e., the product that is unexpectedly the result of the culture of monocytes in said chemicals. For this reason alone the references would be insufficient to support the existence of the claimed cells. However, the cells of the references also display different surface markers, most particularly CD1a, which the claimed cells do not. Accordingly, it is unclear just what the relationship is between the cells of the references and the cells of the instant claims. It is clear, however, that they are produced by a different method and are not the same cells.

Applicant argues that the '756 patent, cited as an example of the production of DC by the culture of monocytes in GM-CSF fails to describe or suggest that the culturing of monocytes with GM-CSF results in the generation of dendritic cells (DCs).

Applicant is advised that in at least Example 1, the method of the '756 patent begins with the same starting material, i.e., cell source, as does the method disclosed in the instant specification. In both case the starting cells are mononuclear cells or "leukocytes", i.e., a mixture of cells that would likely include monocytes, T cells, B cells, stem cells, as well as some immature and mature DCs. The starting cells are cultured in GM-CSF to produce DC precursors. What is now known is that culture of DC precursors in monocyte conditioned medium (medium in which monocytes have been cultured) will result in mature DCs (see for example *Fundamental Immunology*, Paul, ed., page 558). Thus, the method of the reference and the method of the instant specification would result in some mature DCs in a mixed cell population.

Applicant argues that Tables 1, 2, and 3 establish that the claimed MD-APCs are obtained by the disclosed culture system. Regarding Table 1, Applicant argues that the yield of living cells declines as culture continues. "In Table 2, the absence of CD83+ cells clearly shows the absence of "classical" dendritic cells." And "As to Table 3, the MD-APCs are tested for pathagocytic [sic] activity using formalin fixed yeast."

It is the Examiner's position that the Tables clearly disclose mixed cell populations. Regarding Table 1, the specification does not disclose that the results indicate the yield of living cells (or by Applicant's implication, that all living cells were MD-APCs). The specification actually merely discloses a yield. For example the Day 11 yield of 19% or 31% might indicate that 81% or 69% of the cells in the cultures were not MD-APCs, i.e., the results disclose a mixed culture. Regarding Table 2, absent a showing of the actual data, it is well-known in the immunofluorescence art that essentially any desired results (percentage wise) can be achieved depending on the gates that are set. Accordingly, the Table cannot be considered to be data (and thus supporting of the claimed unpredictable cell type) but rather Applicant's interpretation of undisclosed data. Regarding Table 3, the Table clearly indicates that some cells are phagocytic and some are not, a situation that most likely would arise in a mixed cell population.

Applicant argues that "Table 4 provides a direct comparison of the MD-APCs of the present invention and the dendritic cells."

As set forth previously, Table 4 provides no data, but only Applicant's assertion as to the phenotypic characterization of the cells of the instant claims should they actually exist as a single cell type. Regarding amended Table 5, the Table again provides no data but only Applicant's interpretation of undisclosed data, said interpretation being highly subjective.

Applicant then provides two full pages of details for the undisclosed experiments, the results of which are disclosed in Figures 1a and 1b.

It is the Examiner's position that it is inappropriate for Applicant to try to describe experiments that are not adequately disclosed in the specification. The Brief Description of the Drawings merely discloses "Figure 1a represents the allogenic T cell proliferation induced by MD-APCs of the invention recovered in the presence of histamine (10^{-6} M) and cimetidine (10^{-6} M) as adjuvant, with or without GM-CSF (500 U/ml) comparing to standard

macrophages produced only in the presence of the GM-CSF (500 U/ml). Figure 1b represents the stimulation by MD-APCs recovered in the presence of GM-CSF or GM-CSF + IL-13." This limited description is simply inadequate to assess the value of the asserted experiments. Applicant's attempt to describe the experiments after-the-fact comprises an attempt to indirectly introduce new matter into the specification (or at least into the examination process) and accordingly, will not be considered.

It is noted that Applicant has failed to address a number of the issues raised in the previous rejection. Specifically, the disclosure at page 5 wherein it is disclosed that only a small percentage of the cells in culture need display particular surface antigens, used to indicate the presence (or absence) of specific cell types. For example, only 10% of the cells need express CD14 on their cell surface, and only 30% of the claimed cells in a culture need possess high phagocytic capacity. It is clear then that in this disclosure the specification is describing a mixed culture of different cell types and not the specific cell of the instant claims. This disclosure indicates a mixed cell population. It must also be noted that the claimed cells are not even necessarily "monocyte-derived" given the fact, as set forth above, that the starting cells comprise a mixed population of "leukocytes" and there is no demonstration that it is the monocytes in said mixed population that differentiate into the MD-APCs of the claims.

Additionally, Applicant has not addressed the breadth of the claims, i.e., as now recited, MD-APCs differentiating "in the presence of lymphocytes, GM-CSF and at least one ligand having a receptor on the surface of monocytes". As set forth previously, this would indicate that numerous ligands are capable of inducing this unexpected capacity. Yet only a single combination of histamine and cimetidine is disclosed. While the specification lists a number of other chemicals assertedly capable of inducing the same unexpected, and thus unpredictable, effect, absent a showing of said capability, or at minimum an explanation of the mechanism by which said chemicals would be expected to achieve said capacity, the claim must be considered highly unpredictable. Given said unpredictability, it must be concluded that the making of the MD-APC of the instant claims would require undue experimentation.

6. The following are new grounds of rejection necessitated by Applicant's amendment.

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 44, 46-47, 49-51, 53-55, 60-61 and 88 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically:

A) The recitation of "higher phagocytic properties of formalin fixed yeast and higher ability for stimulation of allogenic T lymphocytes" in Claims 44, 55, and 88 is vague and indefinite as the claims recite no specific amount "higher". Accordingly, the metes and bounds of the claims cannot be established.

B) In Claims 44, "in the present of" would properly be "in the presence of".

9. No claim is allowed.

10. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dr. Gerald Ewoldt whose telephone number is (703) 308-9805. The examiner can normally be reached Monday through Thursday and alternate Fridays from 7:30 am to 5:30 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application

should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Papers should be faxed to Technology Center 1600 at 703-872-9306 (before final) and 703-872-9307 (after final).

G.R. Ewoldt, Ph.D.
Primary Examiner
Technology Center 1600
May 5, 2003